



- CZ 3. The purified polypeptide of claim 1, wherein the recognition site is a peptide sequence selected from the group consisting of DEVD (SEQ ID NO: 21), VEHD (SEQ ID NO: 23, wherein X is H), LETD (SEQ ID NO: 24) LEHD (SEQ ID NO: 22, wherein X is L or SEQ ID NO: 25) IEPD (SEQ ID NO: 16), DETD (SEQ ID NO: 17), WEHD (SEQ ID NO: 22, wherein X is W or SEQ ID NO: 18), YVAD (SEQ ID NO: 19), VEID (SEQ ID NO: 23, wherein X is I), and any combination thereof.

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**REMARKS**

A. **Regarding the Amendments**

Claims 1 and 3 have been amended as set forth in the attached "Version With Markings To Show Changes Made". As amended, the claims are supported by the specification and the original claims. Applicant submits that the amendments to the claims are for clarity and should not be construed as amendments affecting patentability under *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir. 2000) (en banc). Thus, upon entry of the amendments, claims 1 and 3 to 8 will be pending.

B. **Objections to the Drawings**

The drawings have been objected to by the Draftsman under 37 CFR 1.84. Applicant respectfully disagrees with the comments under sections 6 and 11 of the "Notice of Draftperson's Patent Drawing Review" form. Reconsideration of these objections is therefore respectfully requested.

Figure 1 is objected to under 37 CFR 1.84(h)(2), as "[b]rackets [are] needed to show figure as one entity." Applicant respectfully disagrees. Figure 1 is a schematic diagram of the process of the invention. As set forth, the figure demonstrates the process and the arrows identify the direction of the process. It is submitted that the figure is a single entity, as filed. Therefore, it is respectfully submitted that brackets are not needed to show the figure as one entity. Withdrawal of the objection to Figure 1 under 37 CFR 1.84(h)(2) is respectfully requested.

Figures 3, 4 and 5 are objected to under 37 CFR 1.84(m), as the “[s]olid black shading [is] not permitted.” However, it is respectfully submitted that 37 CFR 1.84(m) specifically states, “Solid black shading areas are not permitted, *except when used to represent bar graphs or color.*” (Emphasis added.) It is respectfully submitted that Figures 3, 4 and 5 are all bar graphs and, thus, the use of solid black shading is permissible. Withdrawal of the objection to Figures 3, 4 and 5 under 37 CFR 1.84(m) is respectfully requested.

Figures 1 to 6 are objected to under 37 CFR 1.84(p) as the “[f]igure legends are poor.” Applicant respectfully submits that the handwritten figure legends will be replaced with appropriate plain and legible characters when the amended drawings are submitted.

With regard to the time for filing the amended drawings, the reverse side of the “Notice of Draftperson’s Patent Drawing Review” form contains “Information on how to effect drawing changes.” In this section, it is stated that “acceptable corrected drawings must be submitted within the three-month shortened statutory period set in the Notice of Allowability (PTOL-37).” Applicant respectfully submits that acceptable drawings will be submitted before the end of that period. However, as the application has not yet been deemed in condition for allowance, Applicant defers submission of the amended drawings until that time.

#### C. Claims Objections

Claim 3 of the present application was objected to as not containing sequence identification numbers in reference to the sequences contained therein. As set forth above, claim 3 has been amended to contain such sequence identifiers. As such, it is respectfully requested that the objection be withdrawn.

#### D. Rejection Under 35 U.S.C. § 112

Applicant respectfully traverses the rejection of claims 1-3 and 6-8 under 35 U.S.C. § 112, first paragraph, as containing subject matter allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time

the application was filed, had possession of the claimed invention. Applicant respectfully requests withdrawal of this rejection, as set forth below.

In particular, it is alleged in Paper No. 17 that there is no limitation to the structure or source of the polypeptide of claims 1 and 2. It is alleged that the claims encompass a genus of polypeptides of unlimited structure described by the function of having decreased luciferase activity upon cleavage by a protease. It is further alleged that the specification describes only one type of *Renilla* luciferase modified with several recognition sites is not representative of the species that have different structures but the same function. Applicant submits that the present application contains an adequate written description of the structure and source of the claimed polypeptide of claims 1 and 2. The specification, for example, discusses various *anthozoans*, in addition to *Renilla*, which are bioluminescent and contain luciferase, for example, at page 5, lines, 15-21.

In the interest of advancing prosecution of the present application, Applicant has amended claim 1 to incorporate claim 2. As such, the claimed peptide is characterized as having *Renilla* luciferase activity.

It is therefore respectfully requested that the rejection of claims 1 and 2 under 35 USC §112, first paragraph be removed. It submitted that as amended, claim 1 adequately sets forth both the structure and function of the claimed polypeptide. As a *Renilla* luciferase, the from which the polypeptide is derived is specified and the function of having luciferase activity that decreases upon protease cleavage is specified. As amended, the claim is not "drawn to a genus of polypeptides of unlimited structure described only by the function of having a decrease in luciferase activity upon cleavage by a protease." Therefore, amended claim 1 meets the written description requirement of 35 U.S.C. §112, first paragraph. Accordingly, removal of the rejection is requested.

Similarly, the rejection of claims 3, 7 and 8 under 35 USC §112, first paragraph is traversed. Amendment of claim 1, as discussed above, also limits dependent claims 3, 7 and 8 to

*Renilla* luciferase. As such, the structure and source of the luciferase are adequately limited. Accordingly, the removal of the rejection of claims 3, 7 and 8 as allegedly failing to meet the written description requirement of 35 USC §112, first paragraph is respectfully requested.

**E. Rejection Under 35 U.S.C. § 102**

Applicant respectfully traverses rejection of claim 1 under 35 U.S.C. 102(b) as allegedly anticipated by Thompson, et al. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (In re Spada, 15 USPQ 2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 2d 1566 (Fed. Cir., 1990). It is respectfully submitted that Thompson does not teach all of the elements of the present claims.

The Examiner's attention is respectfully drawn to amended claim 1, which recites that the claimed polypeptide has *Renilla* luciferase activity and a recognition site specifically cleavable by a protease, wherein cleavage results in a decrease in luciferase activity. The Thompson reference discusses the effects of mutation of various regions of firefly luciferase on light emission. The luciferase taught in Thompson is not *Renilla* luciferase, nor, in a discussion of "related enzymes" in Fig. 3 of Thompson is *Renilla* luciferase mentioned.

Structurally, *Renilla* luciferase differs from the *P. pyralis* luciferase of the Thompson reference. Were *Renilla* luciferase added to the figure comparing the sequence for *P. pyralis* to various luciferases, it would be seen that from positions 193 to 224, only three positions of *Renilla* luciferase are the same as *P. pyralis*. These are positions 194 (L), 205(P) and 213(R). *Renilla* luciferase does not possess any of the amino acids indicated as "absolutely conserved" among the luciferases in Fig. 3 of Thompson. Additionally, an increase in the half-life for light emission decay in Thompson was observed with a S198T mutation in the *P. pyralis* luciferase. However, the amino acid in position 198 of the *Renilla* luciferase is Glu. As Thompson does not teach *Renilla* luciferase as a polypeptide that has luciferase activity and a recognition site specifically cleavable by a protease, wherein cleavage results in a decrease in luciferase activity, it

does not anticipate the present invention. As such, it is respectfully requested that the rejection of claim 1 as anticipated under 35 USC §102(b) be removed.

**F. Rejection Under 35 U.S.C. § 103(a)**

Applicant respectfully traverses the rejection of claims 1-3 and 6-8 under 35 U.S.C. 103 as allegedly obvious over Lorenz, et al., in view of Xu, et al. Initially, the Examiner's attention is respectfully drawn to amendment to claim 1 and the cancellation of claim 2. The applicability of the rejections will be addressed as if the amended claims had been rejected.

It is alleged in Paper No. 17 that the Lorenz reference teaches that *Renilla* luciferases may be used as a marker in mammalian cells. However, it is stated that Lorenz does not anticipate the present invention because Lorenz "does not teach a *Renilla* luciferase having DEVD, the recognition cleavage site of caspase-3." (Paper No. 17, page 5.) Applicant respectfully submits that the Lorenz reference also does not teach a polypeptide with *Renilla* luciferase activity with any recognition site specifically cleavable by protease, wherein cleavage results in a decrease in luciferase activity.

The Xu reference discusses a green fluorescent protein (GFP) linked to a blue fluorescent protein (BFP) via an 18 amino acid region containing a DEVD sequence. The paper examines the effect on the fluorescence energy transfer (FRET) between the GFP and the BFP in the presence of caspase-3 and through the subsequent cleavage of the GFP-BFP complex. The Xu reference does not teach or suggest use of a luciferase sequence, nor does it teach or suggest addition of DEVD into any protein to monitor the presence of caspase-3. The Xu reference teaches that a decrease in FRET indicates the presence of caspase-3. The Xu reference does not teach that a decrease in the GFP fluorescence or the BFP fluorescence alone would indicate the presence of caspase-3. Rather the decrease measured is the interaction between the GFP and the BFP. FRET is dependant on the proximity of the GFP and BFP. When separated, through cleavage at the DEVD site, FRET is decreased. In the present invention, the cleavage of the single polypeptide with *Renilla* luciferase activity results in diminished luciferase activity, though

still detectable, as compared with wild type *Renilla* luciferase. As such, the Xu reference does not teach or suggest the elements of the claimed invention not taught in the Lorenz reference. The Xu reference fails to teach or suggest that cleavage by a protease results in a decrease in *Renilla* luciferase activity.

Therefore it is respectfully submitted that the Lorenz reference, alone or in combination with the Xu reference, does not teach or suggest the claimed invention. Neither reference alone or in combination with the other reference teach or suggest that a purified polypeptide with *Renilla* luciferase may be modified to contain a recognition site specifically cleavable by a protease, wherein the cleavage results in a decrease in luciferase activity. Therefore, it is respectfully submitted that the Lorenz reference, in view of the Xu reference does not render independent claim 1, or the claims dependent therefrom, obvious under 35 USC 103(a). Accordingly, removal of the rejection is requested.

As it is submitted that claims 1, 3 and 6-8, as amended, are not obvious for the reasons set forth above, it is respectfully requested that the rejection of claims 4 and 5 as dependent on rejected base claims also be removed.

### CONCLUSION

In summary, for the reasons set forth herein, Applicant maintains that claims 1 and 3 to 8 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

In re Application of Leng  
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Filed: July 19, 2000  
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If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: November 26, 2001



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In re Application of Leng  
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Version with Markings - Page 1



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. A purified polypeptide characterized as having *Renilla* luciferase activity and a recognition site specifically cleavable by a protease, wherein cleavage results in a decrease in luciferase activity.
  
3. The purified polypeptide of claim 1, wherein the recognition site is a peptide sequence selected from the group consisting of DEVD (SEQ ID NO: 21), VEHD (SEQ ID NO: 23, wherein X is H), LETD (SEQ ID NO: 24) LEHD (SEQ ID NO: 22, wherein X is L or SEQ ID NO: 25) IEPD (SEQ ID NO: 16), DETD (SEQ ID NO: 17), WEHD (SEQ ID NO: 22, wherein X is W or SEQ ID NO: 18), YVAD (SEQ ID NO: 19), VEID (SEQ ID NO: 23, wherein X is I), and any combination thereof.